

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/56</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 96/15794</b> <b>(43) International Publication Date:</b> 30 May 1996 (30.05.96)
<b>(21) International Application Number:</b> PCT/US95/15131 <b>(22) International Filing Date:</b> 21 November 1995 (21.11.95)  <b>(30) Priority Data:</b> 08/343,383 22 November 1994 (22.11.94) US  <b>(71) Applicant:</b> BALANCE PHARMACEUTICALS, INC. [US/US]; 842 Las Casas Avenue, Pacific Palisades, CA 90272 (US).  <b>(72) Inventors:</b> SPICER, Darcy, V.; 1390 Chamberlain Road, Pasadena, CA 91103 (US). PIKE, Malcolm, Cecil; 27 Virgil Walk, Long Beach, CA 90803 (US). DANIELS, John, R.; 842 Las Casas Avenue, Pacific Palisades, CA 90272 (US).  <b>(74) Agent:</b> SPITALS, John, P.; Robbins, Berliner & Carson, 5th floor, 201 N. Figueroa Street, Los Angeles, CA 90012-2628 (US).		<b>(81) Designated States:</b> CA, FI, JP, NO, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> COMPOSITIONS AND METHODS FOR CONTRACEPTION AND FOR TREATMENT OF BENIGN GYNECOLOGICAL DISORDERS  <b>(57) Abstract</b>  Compositions and methods for use in preventing conception or treating benign gynecological disorders, wherein an effective amount of an antiprogestational agent [e.g., progesterone (progestin, progestogen, gestagen) antagonist or progesterone synthesis inhibitor] administered over a first period of time is combined with an effective amount of a progestogen for a second period of time. The antiprogestational agent is selected from single agents or mixture thereof. The progestogen is selected from single agents or mixtures of natural or synthetic progestogens. The formulations are effective as contraceptive agents and for treatment of benign gynecological disorders including uterine fibroids, premenstrual syndrome, dysfunctional uterine bleeding, polycystic ovarian syndrome and endometriosis.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

COMPOSITIONS AND METHODS FOR CONTRACEPTION AND  
FOR TREATMENT OF BENIGN GYNECOLOGICAL DISORDERS

Background of the Invention

5                This invention relates to compositions and methods useful for  
contraception and for treatment of benign gynecological disorders in mammals,  
especially human females. More particularly, the present invention is directed to  
contraceptive methods and methods of treating benign gynecological disorders and  
preparations for use therein which are effective for reducing exposure to progestational  
10 agents.

              The first progestogen antagonist synthesized and tested was RU 486 [RU  
38486; 17-hydroxy-11-(4-dimethylaminophenyl)-17-(prop-1-ynyl)estra-4,9-dien-3-one;  
beta-[(4-N,N-dimethylamino)-phenyl]-17 $\beta$ -hydroxy-17 $\alpha$ -propynyl-4,9(10)-oestradiene-3-  
one; mifepristone]. Mifepristone has high affinity for the progesterone receptor, with  
15 predominantly antiprogesterone effects. Mifepristone is known to have growth-  
inhibitory effects in breast cancer cells in *in vitro* and *in vivo* preclinical studies and in  
human clinical trials [Klijn, J. G. M. et al. *Cancer Research* 49:2851- 2856 (1989)].  
Other antiprogesterone agents have been synthesized and tested including ZK 98.299  
(onapristone) and ZK 112.993, which also have antitumor efficacy [Michna, H. et al.,  
20 *J. Steroid Biochem. Molec. Biol.* 43:203-210 (1992)].

              Mifepristone is known to be useful as a medical abortifacient (because  
of its antiprogesterone activities) and as a postcoital contraceptive. Mifepristone has  
been evaluated as a potential contraceptive agent using several schedules. A single  
dose of mifepristone late in the menstrual cycle may be a useful contraceptive approach  
25 [Nieman, L. K. et al., *N. Engl. J. Med.* 316:187-191 (1987)].

              Prolonged (i.e., 3 month) administration of 100 mg per day mifepristone  
alone to premenopausal women has been shown to inhibit ovulation and ovarian  
progesterone production, while maintaining early follicular phase levels of estradiol,  
estrone and testosterone [Kettel, L. M. et al. *Fertil. Steril.* 56:402-407 (1991)]. These  
30 effects may be mediated through a progesterone agonist effect of mifepristone on the  
hypothalamic-pituitary unit, although other mechanisms are possible.

-2-

Several new regimens of progesterone antagonists and progestins have been described. One such regimen [Kekkonen, R. et al, *Fertil. Steril.* 53:747-750 (1990)] consists of 25 mg of mifepristone on days 1 to 14 of a 28-day treatment cycle followed by norethisterone on days 15 to 24 of the cycle. A subsequent report  
5 describes a regimen consisting of 25 mg of mifepristone on days 1 to 21 of a 31-day treatment cycle followed by norethisterone 5 mg per day or medroxyprogesterone acetate 5 mg per day taken on days 22 to 31 [Kekkonen, R. et al., *Fertil. Steril.* 60:610-615 (1993)].

These administration sequences are designed to mimic the physiological  
10 secretion of steroids in the menstrual cycle, with a progestational steroid administered over a 10 day period following 14 to 21 days of administration of the progestogen antagonist. With such a regimen, approximately 30% of days are associated with exposure to the progestogen.

PCT Patent Applications WO 93/21926 and 93/21927 to Hodgen (the  
15 entire disclosures of which are hereby incorporated by reference) describes the protracted administration of a progestogen, with administration of an antiprogesterone compound on the 28th or 30th day of the treatment cycle. The contraceptive compositions described by Hodgen provides for an even greater number of days of exposure to the progestogen component than in the normal menstrual cycle.

20 The breast has a tightly regulated pattern of growth primarily under the control of steroid hormones. The effects of steroid hormones on the normal breast are increasingly well understood. Estrogen induces some breast epithelial proliferation, but estrogen and progesterone together produce even greater cell proliferation [Pike, M.C. et al., *Epidemiol. Rev.* 15:17-35 (1993)]. In non-pregnant premenopausal women the  
25 breast epithelium undergoes repetitive periods of cell proliferation and cell loss secondary to cyclic ovarian activity. In the terminal duct lobular unit (TDLU) of the premenopausal breast, cell proliferation is low during the follicular phase of the menstrual cycle. Following ovulation, progesterone is produced by the corpus luteum and TDLU cell proliferation increases two- to three-fold over follicular levels [Pike et al. (1993), *supra*]. Consistent with the breast cell proliferation rates, the size and  
30 number of terminal ductules peak during the late-luteal phase [Longacre, T.A. &

-3-

Barlow, S.A., *Am. J. Surg. Path.* 10:382-393 (1986)]. If fertilization and pregnancy do not ensue, progesterone levels fall, the rate of breast cell division decreases, and a wave of cell death by apoptosis follows the peak in cell proliferation [Anderson, T.J. et al., *Br. J. Cancer* 46:376-382 (1982)].

5 Proliferating cell populations are more susceptible to carcinogenic effects, and the rise in cancer risk associated with cell proliferation is secondary to an increased chance of mutation and loss of tumor suppressor genes [Preston-Martin, S. et al., *Cancer Res.* 50:7415-7421 (1990)]. Thus, breast cancer risk would be predicted to increase the greatest during periods of exposure to both estrogen and progesterone,  
10 as in the premenopausal period or in women receiving combined oral contraceptives (COCs); less during periods of exposure only to estrogen, as in postmenopausal women receiving estrogen replacement therapy (ERT) or in obese postmenopausal women; and least during periods of exposure to very low levels of both hormones, as in non-obese postmenopausal Asian women.

15 The heretofore-identified regimens comprising administration of an antiprogestational agent in sequence with a progestogen are thus not entirely satisfactory. In particular, they result in exposure to progestogens for a period of time similar to a normal menstrual cycle, and to a similar or greater amount of progestational action. As such, they may result in a breast cancer risk similar to or possibly greater  
20 than that of a normal ovulating woman.

U.S. Patent No. 5,211,952 to Spicer et al. (the entire disclosure of which is also hereby incorporated by reference) describes administration of a progestational agent every two months to six months, with administration of a gonadotropin hormone releasing hormone and an estrogen.

25 It is an object of the present invention to provide regimens for contraception and the treatment of benign gynecological disorders which would obviate the problems attendant to the use of existing methods of birth control and treatment regimens.

In particular, it is an object of the present invention to reduce the risk  
30 of adverse consequences associated with the heretofore known methods.

-4-

**Brief Description of the Invention**

In accordance with the present invention, there are provided methods for contraception and for treating benign gynecological disorders which comprise administering over an extended period of time (on the order of about 6 weeks to about 5 26 weeks) an amount of an antiprogestational agent (e.g., a progestational antagonist or progesterone synthesis inhibitor) effective at suppressing ovulation or ovarian progesterone production and/or at blocking the effects of progesterone, followed by a short-term administration (on the order of about 5 to 21 days, preferably 10 to 15 days) of an amount of a progestational steroid effective to counteract the possibility of 10 endometrial hyperstimulation, hyperplasia or carcinoma which may develop during prolonged therapy with estrogenic steroids. The reduction in the amount of progestogen administered has the effect of reducing the projected rate of breast cancer incidence, as well as treating or reducing the incidence of various benign gynecological disorders.

15

**Detailed Description of the Invention**

The present invention eliminates problems inherent in the heretofore-proposed gonadotropin releasing hormone plus estrogen and periodic progestin treatment. The antiprogestational agents may be administered by mouth. Furthermore, 20 as the antiprogestational agents do not suppress ovarian estrogen and androgen production, there is no need for replacement of these steroid hormones.

Pursuant to one preferred embodiment of the present invention, the contraceptive or treatment regimen comprises either a daily administration or a formulation designed for continuous use over an extended period of time. Typically, 25 the formulations of the invention are effective for use over at least about 6 weeks. Depending on the composition, the inventive formulation may be effective for as long as about 6 months. It is presently preferred that the formulation be effective over about a 2 to 3 month period.

For purposes of the present invention, an "antiprogestational agent" is 30 defined as a composition which impedes or eliminates the effects of progesterone in a patient being treated therewith. This may be effected in one of two general ways. A

-5-

progesterone antagonist interacts with progesterone receptors to prevent a progestogen's biological effects on known target tissues such as breast, myometrium and endometrium. Progesterone antagonists may additionally suppress ovulation and ovarian progesterone production. Progesterone synthesis inhibitors block the ovarian  
 5 production of progesterone without necessarily blocking the effect of the progestogen at the tissue level.

A number of compounds have been developed to act as progesterone antagonists, including but not limited to the following: mifepristone (RU 486; 17-hydroxy-11-(4-dimethylaminophenyl)-17-(prop-1-ynyl)estra-4,9-dien-3-one $\beta$ -[(4-N,N-  
 10 dimethyl amino)-phenyl]-17 $\beta$ -hydroxy-17 $\alpha$ -propynyl-4,9(10)-oestradiene-3-one); onapristone (ZK 98.299); ZK 112.993; Org 31710 [(6 $\alpha$ ,11 $\beta$ ,17 $\beta$ )-11-(4-NMe<sub>2</sub>,-phenyl)-6-Me-4',5'-dihydrospiro[oestra-4,9-diene-17,2'(3'H)-furan]-3-one]; Org 33628 [(11 $\beta$ ,17 $\alpha$ )-11-(4-acetylphenyl)-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-one]; Org 31806 [(7 $\beta$ ,11 $\beta$ ,17 $\beta$ )-11-(4-NMe<sub>2</sub>,-phenyl)-7-Me-4',5'-dihydrospiro(oestra -4,9-diene-  
 15 17,2'(3'H)-furan)-3-one]; and lilopristone (ZK 98734). These and other potentially useful agents are described in, e.g., the following publications: the aforementioned PCT applications WO 93/31926 and WO 93/31927; U.S. Patent 4,386,085; U.S. Patent 4,027,019; U.S. Patent 4,000,273; U.S. Patent 3,890,356; U.S. Patent 3,622,622; U.S. Patent 3,983,144; U.S. Patent 3,462,466; U.S. Patent 3,790,564; U.S. Patent  
 20 4,231,946; Pollow, K. et al., *Contraception* 40:213-32 (1989); and Michna et al. (1992), *supra*, the entire disclosures of which are hereby incorporated by reference. The progesterone antagonist mifepristone is commercially available in a number of countries and is in clinical trials in the United States.

Also contemplated as within the scope of the present invention are  
 25 inhibitors or antagonists of progesterone synthesis, which block the production of progesterone. Examples of suitable progesterone, synthesis inhibitors include, but are not limited to, the following: trilostane, epostane, azastene and cyanoketone [PCT applications WO 93/1926 and WO 93/31927; Haider, S. & Inbaraj, R.M., *Gen Comp Endocrino* 73, 92-5 (1989)].

30 To identify additional antiprogestational agents suitable for use in the compositions and methods of the present invention, it is further possible to employ

-6-

heretofore-known biological assays for such agents. An exemplary assay is described in Michna, H. et al., *J. Steroid Biochem. Molec. Biol.* 38:359-365 (1991) for progesterone antagonist. In this bioassay rats are subjected to ovariectomy on day 1. On day 8 the experimental rats are administered estrone, progesterone and the  
5 progesterone antagonist daily. On day 11 the animals are sacrificed and the number of tubular alveolar buds in the inguinal mammary gland counted in a whole mount preparation using a 40-fold magnification. Potent progesterone antagonists inhibit the proliferative action of the progesterone and reduce the number of tubular alveolar buds by 30 to 35 % or more.

10 A suitable dose of the antiprogestational agent may be readily identified. For antagonists that block ovulation and for progesterone synthesis inhibitors, the lowest dose of the composition that eliminates the known rise in serum progesterone during the second half of the normal menstrual cycle is appropriate. With reference to the exemplary antagonist mifepristone (RU486), this dose would be in the range of  
15 about 10 to about 100 mg per day. Similarly, with reference to the exemplary progesterone synthesis inhibitor epostane, this dose would be in the range of about 600 to about 1000 mg per day. For antagonists that do not block ovulation, a dose of the composition that eliminates the antimitotic effects of progesterone and decidualization of the endometrium during the second half of the normal menstrual cycle would be  
20 appropriate [Ferenczy, A. et al., *Am J. Obstet Gynecol* 133, 859-67 (1979)].

As would be readily understood by those working in the field, the amount of the antiprogestational agent effective to achieve the desired results may readily be determined empirically with respect to any given antiprogestational agent and for any given mammal. The effective dose ranges, as well as being compound specific,  
25 may also depend upon patient characteristics, such as age and weight. Further, the effective amount of the antiprogestational agent also depends upon route of administration. In general, it is expedient to administer the active antiprogestational agent in an amount between about 0.001 and 10 mg/kg of body weight per day.

The second component of the invention is a progestogen (progestational  
30 agent). Unlike the antiprogestational agent, which is administered at a continuous level for an extended period of time, the progestogen is administered in amount sufficient to



-7-

provide suitable systemic levels for only a second, more limited period of time. Typically, the progestogen is administered for a period of time on the order of 5 to 21 days, and preferably 10 to 15 days. The progestogen is provided in an amount effective to inhibit ovulation (and the rise in serum progesterone) and to minimize or  
5 eliminate the occurrence of endometrial hyperplasia by substantially reducing the possibility of endometrial hyperstimulation which may occur during prolonged treatment with antiprogestational agents without a period of exposure to the beneficial endometrial effects of a progestogen.

Unlike the heretofore-proposed regimens, administration of progestogen  
10 in preferred embodiments of the present invention is generally not repeated every 28-31 days (corresponding to the length of the normal menstrual cycle). Rather, the progestogen component is provided in these preferred embodiments only for a short period of time comprising a portion of each extended treatment regimen cycle. Suitably, an extended treatment cycle in accordance with the present invention  
15 comprises about six weeks to about 26 weeks, and most preferably two or three months, with the progestogen administration comprising only about 5 to about 21 days, and preferably about 10 to about 15 days, of the extended treatment cycle.

Suitable progestational agents (progestogens) for use in accordance with the present invention are described in greater detail in the aforementioned U.S. Patent  
20 No. 5,211,952. These include, but are not limited to, the following: dydrogesterone, ethynodiol diacetate, hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone, norethindrone acetate, norethynodrel, norgestrel, progesterone, megestrol acetate, gestodene, desogestrel, cingestol, lynestrenol, quingestanol acetate and chlormadinone. Typical dose ranges for progestogens depend upon the choice of  
25 steroid and the individual patient. For example, for an adult human female administered norethindrone, typically 1 mg is given by mouth daily during the period of progestogen administration. Alternatively, systemic administration of the progestogen component may be completely avoided, for example by the use of in intrauterine device which releases the progestogen within the uterus. It is presently  
30 preferred that the progestogen be administered at a rate effective to provide serum levels equivalent to serum levels of progesterone of from about 5 to about 20 ng/ml,

-8-

and preferably about 5 to about 15 ng/ml, during the time interval of progestogen treatment.

Administration of formulations in accordance with the present invention in depot form may be effected in a manner well known per se, for example as described in the aforementioned U.S. Patent No. 5,211,952. Similarly, formulations for daily administration may be prepared in a conventional manner by incorporating the active materials into suitable carrier substances. Carrier substances may be organic or inorganic materials which are suitable for enteral or parenteral application and which do not enter into reactions with the active agents. Suitable carrier agents include, but are not limited to, water, alcohols, vegetable oils, polyethylene glycols, lactose, starch, talcum, gelatin, magnesium stearate, sodium lauryl sulfate, etc.

The invention may be better understood with reference to the accompanying examples, which are intended for purposes of illustration only and should not be construed as in any sense limiting the scope of the invention as defined in the claims appended hereto.

#### Example 1

In a contraceptive product for oral administration over a twelve week period, the antiprogestational agent mifepristone is administered as a tablet in a daily dose sufficient to inhibit ovulation (50 mg) for 71 days, followed by the progestogen norethisterone as a tablet in a daily dose sufficient to induce a non-proliferative endometrium (1 mg) for 14 days. Both agents are suitably provided in a convenient pill dispenser package.

#### Example 2

In a contraceptive pellet for subcutaneous administration, mifepristone is administered as a cholesterol pellet to achieve a daily dose of 25 mg for 90 days. The mifepristone/cholesterol pellet is coated with norethisterone in palmitic acid to achieve a daily dose of 0.75 mg per day for 14 days. The superficial norethisterone coat is absorbed over approximately the first 14 days followed by the mifepristone over approximately 90 days.

-9-

## WHAT IS CLAIMED IS:

1. A composition for use in preventing conception or treating benign  
gynecological disorders, comprising:  
an antiprogestational agent at a level effective to inhibit ovulation  
5 over a first period of time; and  
a progestational agent at a level effective to inhibit endometrial  
proliferation over a second period of time, wherein said second period  
of time immediately follows, immediately precedes, or runs concurrently  
with a portion of said first period of time.  
10
2. A composition according to claim 1, wherein said  
antiprogestational agent is selected from the group consisting of mifepristone,  
onapristone, ZK 112.993, Org 31710, Org 33628, Org 31806, lilopristone, trilostane,  
epostane, azastene and cyanoketone.  
15
3. A composition according to claim 1, wherein said  
antiprogestational agent is selected from the group consisting of mifepristone,  
onapristone and ZK 112.993.
- 20 4. A composition according to claim 1, wherein said progestational  
agent is selected from the group consisting of dydrogesterone, ethynodiol diacetate,  
hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone,  
norethindrone acetate, norethynodrel, norgestrel, progesterone, megestrol acetate,  
gestodene, desogestrel, cingestol, lynestrenol, quingestanol acetate and chlormadinone.  
25
5. A composition according to claim 1, wherein said first period of  
time is about 6 weeks to about 26 weeks.
6. A composition according to claim 1, wherein said second period  
30 of time is about 5 days to about 21 days.

-10-

7. A method for preventing conception or treating benign gynecological disorders comprising:

administering an antiprogestational agent at a level effective to inhibit ovulation over a first period of time; and

5 administering a progestational agent at a level effective to inhibit endometrial proliferation over a second period of time immediately following, preceding or running concurrently with a portion of said first period of time.

10 8. A method according to claim 7, wherein said progestational agent is selected from the group consisting of dydrogesterone, ethynodiol diacetate, hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone, norethindrone acetate, norethynodrel, norgestrel, progesterone, megestrol cacetate, gestodene, desogestrel, cingestol, lynestrenol, quingestanol acetate and chlormadinone.

15

9. A method according to claim 7, wherein said first period of time is about 6 weeks to about 26 weeks.

10. A method according to claim 7, wherein said second period of  
20 time is about 5 days to about 21 days.

11. A method according to claim 7, wherein said antiprogestational agent is selected from the group consisting of mifepristone, onapristone, ZK 112.993, Org 31710, Org 33628, Org 31806, lilopristone, trilostane,  
25 epostane, azastene and cyanoketone.

12. A method according to claim 7, wherein said antiprogestational agent is selected from the group consisting of mifepristone, onapristone and ZK 112.993.

30

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US95/15131

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) :A61K 31/56 US CL :514/170, 179, 843 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/170, 179, 843 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) hcaplus, medline- progestational and antiprogestational agents herein as contraceptives or for treatment of gynecological disorders		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Fertility and Sterility, Vol. 53, No. 4, issued April 1990, Kekkonen, R., et al., "Interference with ovulation by sequential treatment with the antiprogestosterone RU486 and synthetic progestin," pages 747-750, see entire document.	1-12
X	Fertility and Sterility, Vol. 60, No. 4, issued October 1993, Kekkonen, R. et al., "Sequential regimen of the antiprogestosterone RU486 and synthetic progestin for contraception," pages 610-615, see entire document.	1-12
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "B" earlier document published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family	
Date of the actual completion of the international search 23 FEBRUARY 1996		Date of mailing of the international search report 04 MAR 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer <i>Richard Freese for</i> M. MOEZIE Telephone No. (703) 308-1235